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Remarks

Applicants appreciate the Examiner's thorough examination of the application. Applicants respectfully requests reconsideration of the claims under examination based on the foregoing amendments to the claims and the following remarks.

Claims 8 and 13 are pending in the application. Claims 8 and 13 are amended. No new matter has been introduced by the instant amendments to the claims. The amendment to claim 8 was made due to canceling of claim 1 which originally was dependent on claim 8. The amendment to claim 13 was made due to incorporating definition of substituents which were defined in cancelled claim 1. Applicants reserve the right to pursue the subject matter cancelled by this or a prior action in this or a subsequent continuation application.

Claims 8 and 13 stand rejected under 35 U.S.C.§103(a) as being unpatentable over Tripathi et al. (IN 186459).

Claims 8 and 13 also stand rejected under 35 U.S.C.§103(a) as being unpatentable over Verma et al. (Indian Journal of Pharmaceutical science, 1989, 51(2), 48-50).

Claim 13 stands rejected under 35 U.S.C.§112, first paragraph, due to lack of enablement.

Rejection under 35 U.S.C.§103(a) over Tripathi

Claims 8 and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tripathi et al. (IN 186459, hereinafter Tripathi). The rejection is respectfully traversed.

The Office Action stated that:

> [t]he difference between the prior art compounds and the compounds of the instant claim are that the compounds of the instant claims are stereochemically pure at *all* the stereocenters representing single optical isomers while the compounds of the

> prior art are mixtures with respect to the stereo centers on the chroman ring system.

In the Tripathi, the asymmetric centers in Chroman nucleus is in state of racemic but asymmetric center in side chain is marked. Whereas in the compounds of the present invention, asymmetric centers at nucleus as well at side chain are well marked (Please see carefully the Tripathi). The compounds of the present invention have three asymmetric centers and all the three asymmetric centers are well defined and therefore compounds are novel. . Usually, when a compound has single asymmetric center, only two isomers are possible. Here, the compounds of present invention have multiple asymmetric centers, i.e.. three asymmetric centers are there and hence **eight isomers are possible**. This is not obvious to skilled artisan. Even the resolving skill for these compounds does not come as ordinary art.

In contrast, the instant invention provides compounds of Formula I in which the stereochemistry of the C3 carbon (bearing the R_2 residue), the C4 carbon (bearing the R_3 residue) and the stereogenic center of the OR_5 residue are specified and thus single enantiomer. More particularly, the compounds provided by claim 1 include those in which R_2 and R_3 are in a *trans* relationship and OR_5 comprises either a *R* or *S* configuration at the side chain (but not a racemic mixture thereof).

The basic concept of the present invention is to show the effect of stereocenter in anti-estrogen side chain. Although Tamoxifen, Raloxifene, centchroman all have similar chains, none of these compounds have a stereocenter in the anti-estrogenic side chain. It is the inventors of the present invention that first introduced a stereocenter in the anti-estrogenic side chain in form of substituted amino-2-hydroxy propyloxy phenyl, and that resulted in a first discovery that the stereo center at anti-estrogenic side chain have increased anti-resorptive and anti-proliferative activity. Beside this, only one particular stereoisomer in the side chain has shown less toxicity (uterotrophic activity). Further, these compounds also show biological activity to certain diseases, such as breast cancer and osteoporosis.

The Office Action merely speculated that one isomer of an enantiomeric mixture is likely to have better interaction with biological macromolecules, but failed to show that those of the present invention actually have better interaction with the target molecule with less toxicity.

For at least the preceding reasons, the Tripathi fails to teach or suggest that specifying the stereochemistry and diastereochemistry of the recited compounds would be desirable. Thus, claim 8 is non-obvious over the Tripathi reference.

As to claim 13, the office action stated :

> The difference between the process in the prior art and the process of the instant claim is the phenolic starting material of the prior art is a diasteromeric, racemic mixture while the phnolic starting material of the instant claim is stereochemically pure isomer. Further, the process in the prior art uses proteic solvent while the instant case uses aprotic solvent for the reaction.
>
> It is well known in the art, because the chiral centers are located away from the roaction centers, the chirality of the reactants would not have any effect on the kinetics or outcome of the reaction. With respect to the solvent medium, it is well known in the art that because of the high temperature and facile nature of phenolic alkylation reaction, the solvent system would not have major effect on the success of the alkylation with no regards to choice of the solvent.

The rejection is respectfully traversed. In the present invention, the chiral center is not located away from the reaction site because the chiral center of epichlrohydrin is important. In addition, the compound of the present invention has three chiral centers. Further, aprotic solvent is used in the present invention since the chiral center does not racemize during the reaction when using those solvents. This is neither taught or suggested by the Tripathi.

For at least the preceding reasons, the Tripathi fails to teach or suggest that the recited method would be desirable. Thus, claim 13 is non-obvious over the Tripathi reference.

Rejection under 35 U.S.C. § 103(a) over Verma

Claims 8 and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Verma (Indian Journal of Pharmaceutical science, 1989, 51(2), 48-50, hereinafter Verma).

The rejection is respectfully traversed. The applicants repeat the argument presented on July 17, 2007 and those presented above in relation to the Tripathi reference. The Verma reference disclosed compounds (compounds are Racemic) having more than one stereogenic center, resulting in not just two enantiomers, but in 2n-1 pairs of enatiomers (where n is the number of stereogenic centers). Unlike in case of enantiomers with one chiral center, the genus contains exactly two species, which is a very small genus, chiral molecules with several stereogenic centers, mere disclosure of the potentially large numbers of candidate molecules does not anticipate the one that is pharmacologically most beneficial.

As stated above, the Verma reference disclosed racemic compounds having three asymmetric centers (three stereo/chiral centers). Thus, it is possibly a mixture of eight enantiomers. The reference defines the stereochemistry of the C3 stereogenic center and does not define the stereochemistry of the C4 carbon or the stereochemistry of stereogenic centers, if any, present on the substituent of the C4 aromatic ring. In other words, there are still two other stereo center present in nucleus (chromane) which are unresolved chiral center. Thus, compounds disclosed in the Verma reference still may be mixture of four isomers.

Further, the Verma reference neither disclosed nor taught which isomer will be active for the intended use of the present invention. Moreover, the Verma reference neither disclosed nor taught the activities such as antiosteoporosis (antiresorptive), antiproliferative, anticancer and hyperlipidaemic properties disclosed in the present application.

In contrast, the instant invention provides compounds in which the stereochemistry of the C3 carbon, the C4 carbon and the stereogenic center of the OR^5 residue are specified and thus single enantiomer. More particularly, the compounds provided by claim 8 include those in which C3 carbon and C4 carbon are in a trans relationship and OR^5 comprises either a R or S configuration at the side chain (but not a racemic mixture thereof).

The compounds of the present invention are designed to show the effect of stereo center in anti-estrogenic side chain. Applicants of the present invention introduced a stereo center in side chain in form of substituted amino 2-hydroxy propyloxy phenyl and that resulted in the unexpected discovery that stereo center at antiestrogenic side chain have enhanced biological activity with less toxicity (uterotrophic activity). The Verma reference neither suggested nor taught the single enatiomer with well defined stereochemistry of the present invention. Moreover, the Verma references neither suggested nor taught that the single enantiomer shows unexpected enhanced activity with low toxicity.

This unexpected enhance activity with low toxicity was proven by the following data obtained by the applicants:

Antifertility activity (MED) 0.025 mg/kg 100 % activity
Estrogenicity (% uterine wt Gain) =11 % .(Estrogenicity is an associated side effect with all Estrogen receptor modulators. By generating single isomers the applicants are able to reduce estrogenicity at 11 % whereas estrogenicity of other isomers is 40 %.)

Osteoporosis activity (In vitro Chick fetal bone culture assay)
T/C ratio = 0.48 This ratio is very good compared to those for prior art compounds
Anti-proliferative Activity in MCF-7 Cell lines: IC50 : 9.0 (μg/ml) (Tamoxifen : IC50 : 13.9 (μg/ml) is taken as control)

For at least the preceding reasons, the Verma reference fails to teach or suggest that specifying the stereochemistry and diastereochemistry of the recited compounds would be desirable. Thus, claim 8 is also non-obvious over the Verma reference.

Thus, the Verma reference neither suggest nor taught any expectation of successfully obtain the claimed compounds with intended effect based on the difference of stereochemistry.

As to claim 13, although the Office Action did not state detailed reason for claim 13, assuming that the reason is similar to that for claim 8, the Verma reference neither suggested nor taught claimed process for the preparation of compounds of formula I. Further, as stated above, there is no suggestion or teachings to use aprotic solvent to prevent being racemized during the reaction in the Verma reference.

For at least the preceding reasons, the Verma reference fails to teach or suggest the process of preparation of compounds of formula I. Thus, claim 13 is non-obvious over the Verma reference.

Rejection under 35 USC §112, first paragraph

Claim 13 has been rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a few compounds of the formula V containing limited number of variables, does not reasonably provide enablement for the wide variety of compounds of the formula V.

The applicants respectfully disagree. The applicant would like to bring the examiners attention to the language of the claim 13. The Office Action recognized the nature of the invention is "the process of preparing chroman compounds of formula V." The compounds of formula V, however, are starting materials, not a target compounds to be prepared. The target compounds can be made by reacting compounds of the formula V with compounds of formula VI, VII, VIII in the presence of bases including K_2CO_3, at temperature ranging between 50 to 120C, obtaining compounds of structure IX (a-c), and reacting compounds of formula IX (a-c) with a nucleophile including an amine of formula X.

Also, this is a method claim, not a compound claim and "as long as the specification discloses at least one method for making and using the claimed invention that bears reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C.112 is satisfied. *MPEP 2164.01(b)*, cited *In re Fisher*, 427 F.2d 833, 839. Here, examples 1-8 discloses how to make compounds of interest by using the claimed method, more than once.

Further, in 2164.01(b) of MPEP, it is stated:

> The Court in *In re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981)

Thus, if the practice of a method requires particular compounds and the compounds are not readily available, a sufficient disclosure of the compound would be necessary. Here, starting materials are well defined both in specification and in claim 13, and actually used in examples 1-8, thus skilled artisan would have easily understand how to make the starting materials since the level of skill in the art is high as recognized by the Office action (page 7, 3rd paragraph), i.e., available for skilled artisan.

Again, this is a method claim, not a compound claim and the specification of the present application teaches those skilled in the art "how to make and use the invention", i.e, how to make and use the method of preparing the compounds of interest with working examples.

Accordingly, the specification enables person skilled in the art to practice the process of making the compounds of the claim.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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